Attorney Docket No. 9022-41 PATENT

In re: Maurer et al. Confirmation No.: 4884
Application Serial No.: 10/767,352 Group Art Unit: 1618
Filed: January 30, 2004 Examiner: Blessing M. Fubara
For: *Oral Compositions of Fenretinide Having Increased Bioavailability and Methods of Using the Same*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

January 26, 2010

Commissioner for Patents
Post Office Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R § 1.132
OF BARRY J. MAURER, MD, PhD

Sir/Madam:

I, Barry J. Maurer, MD, PhD, do hereby declare and say as follows:

1. I received my PhD from California Institute of Technology. I received my medical degree from Wayne State University. I completed an internship at Children's Hospital of Michigan and a residency at LAC/USC Pediatric Pavillion in Los Angeles, CA. I also completed a clinical fellowship in pediatric oncology at Fred Hutchison Cancer Research Center and a research fellowship at Childrens Hospital Los Angeles Research Institute. I am further certified by the American Board of Pediatrics in hematology/oncology. I am currently an Associate Professor of Cell Biology, Pediatrics, and Internal Medicine at Texas Tech University Health Sciences Center in Lubbock, TX.

2. I am a co-inventor listed on U.S. Patent Application Serial No. 10/767,352 (hereinafter, "the '352 application"). I have reviewed the Office Action dated October 27, 2009 issued in association with the '352 application, and I am familiar with the contents

thereof. I have also reviewed U.S. Patent No. 6,352,844 to Maurer et al. (of which I am a co-inventor); U.S. Patent No. 4,874,795 to Yesair; U.S. Patent No. 5,972,911 to Yesair; and U.S. Patent No. 4,665,098 to Gibbs, all of which are cited in the Office Action.

3. My efforts are dedicated to development of new drugs for use against childhood cancers. In particular, neuroblastoma, a type of cancer that affects the nervous system, typically occurs in children under 10 years of age. The previous (and largely ineffective) daily dosage of fenretinide, a synthetic vitamin A derivative, to treat this disease was 60 to 70 hard, oversized capsules. My colleagues and I knew we had to develop something better. Being pediatricians, we know that getting kids to take medicine is a challenge. We have now shown that fenretinide can not only be provided in a more palatable and more convenient way for patients, it can finally be absorbed into the blood at levels capable of shrinking tumors. Additionally, this fenretinide composition can be provided to patients with relapsed neuroblastoma and achieves higher plasma levels than equivalent fenretinide doses previously delivered using corn oil capsules. This new formulation can be further provided with minimal toxicity.

4. We hypothesized that fenretinide/LYM-X-Sorb^{TM} (LXS) oral powder would increase fenretinide plasma levels in relapsed neuroblastoma patients compared to the previously tested fenretinide/corn oil capsule thereby increasing drug delivery to the tumor bed and improving antitumor responses and further facilitating patient compliance with drug administration as compared to the corn oil capsules of conventional fenretinide formulations. Accordingly, a phase I trial in recurrent/resistant neuroblastoma was conducted using a dosing schedule of seven consecutive days of fenretinide/LXS oral powder, every three weeks. Methods are described in greater detail at **Appendix 1**.

5. As shown in the figure provided at **Appendix 2**, results of this study showed that fenretinide/LXS oral powder attained several-fold higher fenretinide plasma levels (peak and trough) compared to equivalent doses of fenretinide previously delivered using corn oil capsules on similar dosing schedules. Additionally, the increased

fenretinide plasma levels did not appreciably increase observed side effects (as noted in Tables 1 and 2 at **Appendix 3**) compared to those reported with conventional high dose oral capsule fenretinide treatment such as reversible liver dysfunction, hypertriglyceridemia, idiosyncratic pseudotumor cerebri, nausea and mild thrombocytopenia. In this study, the most significant side effect was moderate, reversible liver toxicity with minimal hematopoietic side effects as shown in Table 3 of **Appendix 3**.

Of further clinical significance, the fenretinide/LXS oral powder scored more Complete Responses (%) in neuroblastoma tumor than when using the corn oil capsules as shown in the table at **Appendix 4**. Thus, we have demonstrated that obtaining higher drug levels in the blood plasma can, in fact, lead to a better anticancer treatment effect.

6. In summary, the formulations described in the '352 application provide a new formulation for the delivery of fenretinide that yields positive results including increased plasma concentrations. The formulations described in the '352 application represent a new treatment for a childhood cancer that was difficult to treat as well as a new treatment modality for other diseases in which fenretinide may represent a treatment option.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Barry J. Maurer, MD, PhD

Date 1/26/10

APPENDIX 1

METHODS

Patients 30 years of age or younger diagnosed with high-risk neuroblastoma with recurrent/progressive, refractory, or persistent disease after a partial response to frontline therapy, excluding active parenchymal brain or meningeal-based lesions, were eligible. Informed consent approved by a local institutional review board was obtained. Specific disease sites were reviewed only in patients reporting a complete disease response. Specific organ function requirements included absolute neutrophil count 750/μL or greater, and platelets 50,000/μL or higher, creatinine less than 1.5 x for age, and ALT/AST less than 3x normal for age. Postmenarchal females were required to have a negative beta-human chorionic gonadotropin and to utilize contraception.

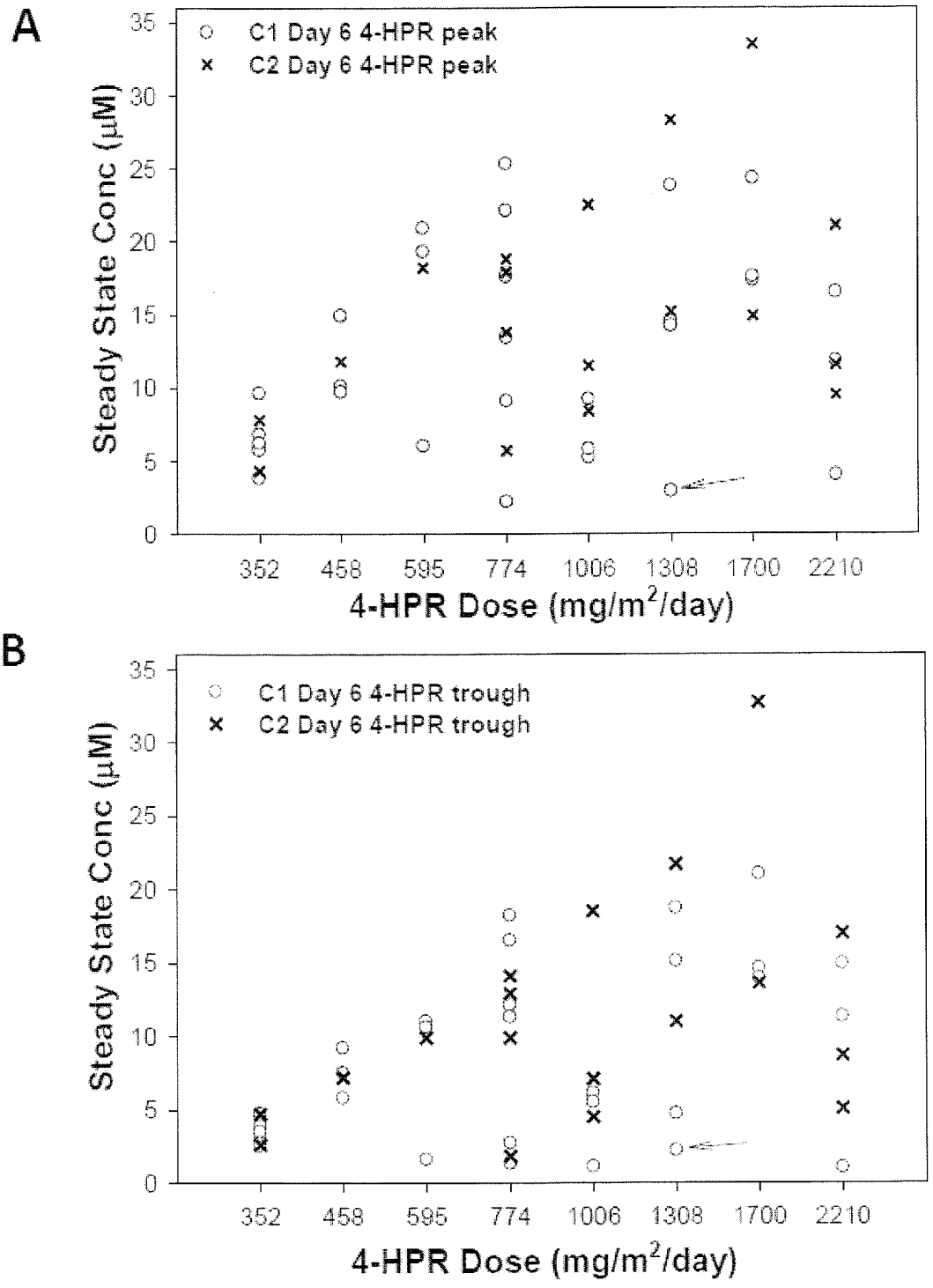
Fenretinide (4-HPR)/LXS oral powder was provided via a Rapid Access to Interventional Development (RAID) grant from the Developmental Therapeutics Program (DTP) of the National Cancer Institute (NCI) to B.J.M. (Study Chair, IND Sponsor) as a powder 3% by weight 4-HPR, 55% wheat flour, 22% LXS lipid matrix (lysophosphatidylcholine, monoglycerides, and free fatty acids), and 20% sucrose. 4-HPR/LXS oral powder was consumed at 352 mg to 2210 mg 4-HPR/m2/day, divided into equal morning and evening doses, for 7 days, every three weeks. Doses were mixed into a liquid nutritional supplement (Slim-Fast®, Unilever) for consumption to ensure uniform delivery between patients. High milk-fat containing foods taken concurrently with daily doses were avoided to reduce possible destabilization of the LXS lipid matrix. Patients were eligible to continue drug until tumor progression.
Dose-limiting toxicity (DLT) was defined as grade 3 or 4 toxicity (National Cancer Institute Common Toxicity Criteria, version 3) excluding grade 3 non-hematologic toxicity, grade 3 nausea/vomiting/diarrhea, and grade 3 hepatic toxicity, that resolved by Day 28 of a course, grade 3 fever or infection, treatable grade 3 headache not due to pseudotumor cerebri, central nervous system toxicity attributable to disease progression, and nyctalopia. Dose escalation was performed using a standard 3 + 3 design with fixed 30% dose escalation increments. The maximum-tolerated dose (MTD) was defined as the maximum dose where at least five of six patients did not demonstrate DLT.

An ophthalmologic examination with visual acuity assessment was required at entry, then every three courses for two examinations, then every four courses. Disease evaluations were done at entry and after courses 2, 4, 6, then every 4th course. Neuroblastoma responses were graded using the revised International Neuroblastoma Response Criteria. Radiological scans and bone marrow slides were centrally reviewed for patients with improving disease, with documentation on two evaluations six or more weeks apart. Grading of metaiodobenzylguanidine (MIBG+) lesions was done using the Curie scale.

4-HPR plasma levels were required and obtained on Course One (Day 0 – 6), pre-dose on Day 0, Hour 0, then at +2 hours (hrs), +4 hrs, 6 hrs, and 8 hrs, after the first dose, on Day 6, pre-am dose, then at +2 hrs, +4 hrs, +6 hrs, and +8 hrs, and on Day 8, once; on Course Two, pre-am dose on Day 0, Hour 0, then at +4 hrs and +6 hrs, Day 2 at +6 hrs after the am dose, and on Day 6, pre-am drug dose, then at +4 hrs and +6 hrs; on Course 6, on Day 6, pre-am drug dose, then at +4 hrs and +6 hrs. 4-HPR, metabolite 4-MPR, and, in some cases, metabolite 4-oxo-4-HPR, were measured as previously described with modification. Briefly, N-(4-ethoxyphenyl)retinamide was added to the plasma samples as an internal standard prior to precipitation with ice-cold acetonitrile. Supernatant was analyzed on an Agilent Technology 1200 system with Photodiode Array Detector set at 354 nm wavelength using an Agilent Technologies ZORBAX Eclipse XDB C18 Column 4.6 x 150mm (3.5 μm). Gradient elution was with methanol and 0.5% acetic acid water at a flow rate of 1.0 ml/min with autosampler temperature at 20 °C. Data current to July, 2009 were used for this report.

Statistical analysis of differences between groups for pharmacokinetic analyses was by one way ANOVA using the Holm-Sidak method with SigmaPlot® 11 software, Systat Software, Inc., San Jose, CA.

APPENDIX 2



4-HPR plasma concentration (A) peaks and (B) troughs measured on the seventh day (Day 6) of Courses One (C1)(o) and Course Two (C2)(X). Arrow indicates Course One values for a patient requiring nasogastric tube delivery for Courses 2+.

APPENDIX 3

Table 1. Dose Limiting Toxicities

Daily Dose ($mg/m_2/day$)	No. Entered	No. Evaluable for Dose Escalation	Patients with Course One DLT	Patients with DLT on Other Courses
352	6	6	1 Grade 3 alkaline phosphatase	0
458	3	3	0	0
595	3	3	0	0
774	6	6	0	1 - Courses 5 and 6, Grade 4 alkaline phosphatase
1006	3	3	0	0
1308	4	3	0	0
1700	3	3	0	1 - Course 2 Grade 3 ALT/AST
2210	4	3	0	0

Table 2. Toxicity Summary Including Unlikely, Possibly, Probably and Definitely Related to Treatment

Dose (mg/m^2/day)	Toxicity Category	All Courses No. Patients with Toxicity Grade			
		1	2	3	4
352 (n=6)	Hepatic	4	1	1	0
	Constitutional Symptoms	1	0	0	0
	Pain	0	2	0	0
	Hemorrhage	1	0	0	0
	Coagulation	1	0	1	0
	Dermatology/Skin	4	1	0	0
	Metabolic/Laboratory	5	0	0	0
	Ocular/Visual	0	1	0	0
	Allergy	1	0	0	0
	Hematologic	2	0	1	0
458 (n=3)	Hepatic	1	1	1	0
	Constitutional Symptoms	1	0	0	0
	Renal/Genitourinary	1	0	0	0
	Infection/Fever/Neutropenia	1	0	0	0
	Coagulation	1	0	0	0
	Dermatology/Skin	2	1	0	0
	Metabolic/Laboratory	1	0	0	0
	Hematologic	2	1	0	0
595 (n=3)	Hepatic	1	1	0	0
	Infection/Fever/Neutropenia	0	1	0	0
	Pain	0	0	1	0
	Gastrointestinal	1	0	0	0
	Coagulation	2	1	0	0
	Dermatology/Skin	0	1	0	0
	Endocrine	1	0	0	0
	Metabolic/Laboratory	0	2	0	0
	Ocular/Visual	1	0	0	0
	Hematologic	2	1	0	0
774 (n=6)	Hepatic	5	0	0	1
	Constitutional Symptoms	0	1	0	0
	Cardiovascular	0	1	0	0
	Infection/Fever/Neutropenia	0	1	1	0
	Pain	2	1	0	0
	Gastrointestinal	4	0	0	0
	Coagulation	3	0	0	0
	Dermatology/Skin	0	2	0	0
	Metabolic/Laboratory	2	2	1	0
	Neurology	1	1	0	0
	Hematologic	3	1	1	0

Dose (mg/m2/day)	Toxicity Category	All Courses No. Patients with Toxicity Grade			
		1	2	3	4
1006 (n=3)	Hepatic	2	1	0	0
	Pain	2	1	0	0
	Gastrointestinal	1	2	0	0
	Coagulation	1	0	0	0
	Metabolic/Laboratory	3	0	0	0
	Allergy	1	0	0	0
	Hematologic	1	1	0	0
1308 (n=4)	Hepatic	2	1	0	0
	Constitutional Symptoms	1	0	0	0
	Pain	2	1	0	0
	Gastrointestinal	1	1	0	0
	Dermatology/Skin	2	0	0	0
	Metabolic/Laboratory	1	1	1	0
	Neurology	0	2	0	0
	Ocular/Visual	2	0	0	0
	Hematologic	2	1	0	0
1700 (n=3)	Hepatic	2	0	1	0
	Constitutional Symptoms	2	0	0	0
	Pulmonary	1	0	0	0
	Infection/Fever/Neutropenia	0	1	0	0
	Pain	2	1	0	0
	Gastrointestinal	2	0	1	0
	Coagulation	2	0	0	0
	Dermatology/Skin	0	1	0	0
	Metabolic/Laboratory	1	2	0	0
	Musculoskeletal	0	1	0	0
	Neurology	1	0	0	0
	Ocular/Visual	1	0	0	0
	Hematologic	1	2	0	0
2210 (n=4)*†	Hepatic	3	0	0	0
	Constitutional Symptoms	1	0	0	0
	Renal/Genitourinary	1	0	0	0
	Infection/Fever/Neutropenia	0	1	0	0
	Pain	1	0	0	0
	Gastrointestinal	2	2	0	0
	Coagulation	1	0	0	0
	Dermatology/Skin	1	2	0	0
	Metabolic/Laboratory	3	0	0	0
	Neurology	1	0	0	0
	Ocular/Visual	0	1	0	0
	Allergy	2	0	0	0
	Hematologic	1	2	0	0

*One patient was able to take only half of Dose One due to nausea and vomiting and was removed from study.

†One patient was diagnosed with a new Langerhans Cell Histiocytosis at disease evaluation after Course Two which also revealed disease progression.

Table 3. All Grade 3 or Grade 4 Toxicities and DLT's

Dose (mg/m2/day)	Patient ID	Any DLT and Grade 3 or 4 Toxicity Observed*					
		Course	Category	Toxicity	Grade	Attribution	DLT
352	N0075	2	Hematologic	Platelet count decrease	3	Possible	No
	N0095	1	Hepatic	Alkaline phosphatase increase	3	Possible	Yes
			Coagulation	PTT	3	Unlikely	No
458	N0110	1	Hepatic	ALT	3	Probable	No
			Hepatic	AST	3	Probable	No
595	N0125	1	Pain	Pain - Chest wall	3	Unlikely	No
		2	Pain	Pain - Chest wall	3	Unlikely	No
774	N0115	5	Hepatic	Alkaline phosphatase increase	4	Possible	Yes
		6	Hepatic	Alkaline phosphatase increase	4	Possible	Yes
		Late	Hepatic	Alkaline phosphatase increase	4	Possible	Yes
	N0134	1	Infection/Fever	Catheter-related infection with normal ANC	3	Unlikely	No@
			Metabolic/Laboratory	Hypokalemia	3	Possible	No
			Metabolic/Laboratory	Hyponatremia	3	Possible	No
			Hematologic	Hemoglobin decrease	3	Possible	No
1308	N0150	1	Metabolic/Laboratory	Hypokalemia	3	Possible	No
1700	N0162	2	Hepatic	ALT	3	Probable	Yes
			Hepatic	AST	3	Probable	Yes
			Gastrointestinal	Diarrhea	3	Definite	No
		Late	Hepatic	ALT	3	Probable	No
			Hepatic	AST	3	Probable	No

*Excludes Unrelated toxicities. @Dose level expanded per consensus of monitoring committee.

APPENDIX 4

Fenretinide Activity in Neuroblastoma

Comparison of Clinical Trial Results using Corn oil Capsule, LXS Oral Powder, and Intravenous emulsion formulations of fenretinide

Study	Phase	Dose Form	Max Plasma Level Obtained (μM)	# Evaluable Patients	# Complete Tumor Response	PR/SD
CCG 09709	I	Capsule	8 - 10	30	1	13
COG ANBL-0321	II	Capsule	6 - 9	58	2	12
NANT 2004-04	I	LXS Oral Powder	15 - 20	30*	4*	6*
NANT 2004-03	I	Intravenous	In progress	In progress	NA	NA

*all responses in ≥ Dose Level 4, n = 18
PR = partial tumor response;
SD = stable disease

Fenretinide/LXS oral powder obtained higher drug levels in blood plasma and scored more Complete Responses (complete tumor disappearance) than the Corn oil capsule formulation despite being tested in fewer total patients (4/30 vs. 3/88).